Paradigms and perspectives

AllergoOncology: IgE- and IgG4-mediated immune mechanisms linking allergy with cancer and their translational implications

Erika Jensen-Jarolim, MD,a,b Michelle C. Turner, PhD,c,d,e,f and Sophia N. Karagiannis, PhDg,h Vienna, Austria; Barcelona and Madrid, Spain; Ottawa, Ontario, Canada; and London, United Kingdom

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Since the detection of specific IgE in allergy, its potential role in cancer has been investigated and prompted the definition of the field of AllergoOncology. Most recent developments are collected in a position paper by the European Academy of Allergy and Clinical Immunology.

IgE AND CANCER

IgE is an antibody with properties distinct from those of other isotypes, specifically in terms of its affinity for its cognate Fc receptor FcεRI. FcεRI-IgE immune complex formation can activate potent effector cells normally associated with acute and chronic allergic responses. IgE effector cells, such as eosinophils, mast cells, and macrophages, are also known to infiltrate tumors; tumor-associated tissue eosinophilia (TATE) or tumor-associated macrophages (TAMs, which can constitute up to 50% of a tumor mass and can be alternatively activated, M2) are characteristics of tumor inflammation. While intratumoral or stromal mast cells have been correlated with tumor promotion, signs of mast cell degranulation, normally associated with IgE–immune complex formation, have been correlated with a more favorable prognosis. Mast cells are a prominent source of the proinflammatory cytokine TNF-α, which is known to promote antitumor immunity. Other released mediators turn on acute (histamine) or chronic (eg, slow-reacting substance of anaphylaxis and cytokines) inflammation and promote amplification of innate effector mechanisms. These cells can harbor cytotoxic and phagocytic potential, which could be directed against tumors.

The potential efficacy of IgE antibodies engineered to recognize tumor antigens is exemplified in vitro by using cell-based assays, suggesting that IgE directed against tumor antigens engenders antibody-dependent cell-mediated cytotoxicity (ADCC) by human monocytes, whereas, through its interaction with FcγRs, IgG1 of the same antigen specificity can instruct the same cells to trigger antibody-dependent cell-mediated phagocytosis (ADCP). IgE anti-cancer antibodies engage subsets of FcεRI-expressing effector cells to mediate ADCC against tumors without the inhibitory Fc receptor signals known to limit IgG effector functions in the tumor microenvironment. IgE is cross-linked by densely packed tumor antigens but not by soluble monovalent antigens, forming tumor-associated molecular patterns (TAMPs) on a cancer cell surface and therefore triggering effector cell activation at sites where antitumor immunity is needed (Fig 1). Therefore it is tempting to speculate that IgE antibodies directed against tumor antigens can propagate alternative or complementary antitumor functions to those of clinically available IgG mAbs specific for tumor antigens, such as epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2). Prompted by promising preclinical studies in numerous in vivo models of cancer and in nonhuman primates, the first clinical trial of an antitumor IgE antibody in patients with cancer is ongoing (NCT02546921).

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Corresponding author: Erika Jensen-Jarolim, MD, Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University Vienna, Währinger G. 18-20, 1090 Vienna, Austria. E-mail: erika.jensen-jarolim@medunwien.ac.at.

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Corresponding author: Erika Jensen-Jarolim, MD, Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University Vienna, Währinger G. 18-20, 1090 Vienna, Austria. E-mail: erika.jensen-jarolim@medunwien.ac.at.

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Allergy is characterized by TH2-dominant immune responses, featuring IL-4, IL-13, and thymic stromal lymphopoietin upregulation. Because these mediators can be observed in cancer tissues, strategies to activate these responses could in principle promote isotype switching to antitumor IgE and also IgE/FcεRI-associated cross-presentation by dendritic cells, resulting in activation of CD4⁺ T cells but also of CD8⁺ cytotoxic T lymphocytes. Therefore although TH1 responses and a strong branch of CD8⁺ cytotoxic T lymphocytes are generally desired in oncology, activation of classical TH2 cells has also been associated with improved survival. On the other hand, TATE and TAMs, especially those alternatively activated M2 populations, might be signs of a TH2-biased immune response unable to restrict cancer growth. Evidence of an alternative TH2 inflammatory milieu featuring enhanced IL-10 rather than IL-4 in patients with many cancers, including melanoma, can influence class-switching away from IgE and perhaps favor expression of isotypes with more restricted effector functions, such as IgG4 or IgA.

Therefore the question remains whether allergies in general can protect against cancer. Epidemiologic meta-analyses suggest a strong inverse association between allergy and atopy and risk of glioma, pancreatic cancer, and childhood leukemia, although there are limitations in previous studies related to measures of allergy history and latency period. Inverse associations of prediagnostic IgE and cancer risk have also been reported overall, as well as for glioma specifically, but fewer associations have been reported at other cancer sites. Prospective studies in large cohorts are required to further understand the potential role of IgE and other immunologic parameters in cancer risk and potential underlying biological mechanisms to be able to better harness “classical” TH2 immune responses and IgE against cancer.
around tumors. Tumor cells and infiltrating immune cells, such as regulatory T cells and likely regulatory B cells, can secrete cytokines, such as TGF-β and IL-10, which support immune tolerance and moderate immune surveillance, hindering any antitumor activities of effector cells. Checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) or cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) to unleash the cytotoxic potential of a patient’s T-cell immunity are major breakthroughs in clinical oncology, even at the cost of severe systemic autoimmunity.

In contrast, allergen immunotherapy attempts to re-establish immune tolerance to the allergen. A hallmark of allergen immunotherapy is IgG4, which is supported by IL-10–producing cells, such as regulatory T and regulatory B cells. IgG4 antibodies can block allergic responses through various mechanisms, such as through interacting with the inhibitory FcγRIIB on B cells to block IgE synthesis. IgG4 is also a special antibody isotype devoid of complement activation properties and with impaired effector functions. These characteristics might be due to hinge region sequences that render IgG4 prone to Fab arm exchange and formation of naturally bispecific antibodies less able to be cross-linked by an allergen and therefore resistant to allergen-associated molecular patterns (AAMPs) (Fig 1). Furthermore, IgG4 might repolarize M2a macrophages to the immunosuppressive phenotype M2b, which could be responsible for increased IL-10 secretion. Strikingly, IgG4 is expressed in tissues from patients with malignancies such as melanoma, in whom it can impair antitumor immunity and correlates with shorter survival and disease progression. There is also increasing evidence to support positive correlations between IgG4-related diseases, such as sclerosing cholangitis associated with autoimmune pancreatitis, with enhanced cancer risk, including more recent long-term follow-up investigations. However, the antigen specificities of IgG4 antibodies are unclear. Notably, higher levels of IgE and IgG4 recognizing the cancer antigens EGFR and HER2, but not carcinoembryonic antigen, were detected in the sera of patients with cancer compared with allergic patients. Therefore the tumor microenvironment could favor class-switching to IgG4 within a “modified TH12 response” in a process that features high similarities to those reported in patients with cat allergy. Elucidating the conditions promoting IgG4 isotype switching still requires the design of immunologically relevant animal models other than rodents, potentially monkeys or canines.

Hence the opposite from allergen immunotherapy might be required in cancer treatment, i.e., reduction of “alternative” TH12 isotypes, such as IgG4, in situ and simultaneous promotion of immune activatory IgG antibodies against cancer antigens. It might be envisaged that cancer immunotherapy strategies could aim at shifting existing IgG4 responses to IgE through sequential isotype switching, perhaps with the aid of adjuvants.

CONCLUSION
Harnessing components of the “classical” TH2 humoral immunity against tumors might offer novel oncological treatment avenues. Thus AllergoOncology might provide strategies that complement existing and emerging immuno-oncology therapies.

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REFERENCES